REMARKS

Claims 1-31 are pending. In response to a restriction requirement, claims 7 and 10-31 were previously withdrawn. Claims 1-6, 8, and 9 are presently under examination. Claims 1-6 and 8 stand substantively rejected, while claim 9 is objected to based on formal grounds. In the instant amendment, claims 7 and 10-31 are canceled, and claims 1, 2, and 9 are amended. Re-examination and reconsideration of the claims is respectfully requested.

The paragraph numbering below follows that of the Office Action (Paper Number 15).

Informal Objection

¶5. Claim 9 was objected to as allegedly containing a grammatical error. Applicant has amended claim 9. Withdrawal of this objection is respectfully requested.

Rejections Under 35 U.S.C. §112

¶8. Claims 1-6 were rejected under 35 U.S.C. §112, first paragraph, on the grounds that, while the specification enables a method of preventing autoimmune diabetes with an agonist antibody to CD28, it allegedly does not provide enablement for a method of preventing the development of other autoimmune diseases or a method of employing any CD28 agonist.

With respect to applicability of the claimed method to autoimmune diseases other than autoimmune diabetes, the Examiner argues that not all autoimmune diseases would be viewed by the skilled artisan as likely to benefit from stimulation of a TH2 type of immune response.

It is clear from discussion at various places in the specification as filed that the method of the invention involves activation of the CD28 signalling pathway (page 15, lines 17-21), with down regulation of Th1 cell function and promotion of Th2 cell function (page 17, lines 20-28). One of skill in the art would therefore be well aware that such a treatment is applicable to autoimmune diseases associated with increased Th1

cell activity, described by the Examiner as "Th1 type" autoimmune diseases, which comprise the vast majority of autoimmune diseases. For further clarification, claim 1 has been amended to indicate this.

The Examiner further argues that studies of blocking B7-1 or B7-2 can be extrapolated to conclusions regarding the effects of CD28 activation. The applicant emphatically disagrees and submits that antagonising B7-1 or B7-2 is a completely different process from agonising or activating CD28 and that no conclusions can be drawn from the B7-1/2 studies regarding likely inconsistencies in outcome from activating CD28 in different diseases.

The Examiner also argues that since different autoimmune diseases involve different antigens, with different time courses, the time for therapeutic intervention could not be determined.

The treatment method of the invention, as described in the specification as filed, is optimally employed in the early stages of the autoimmune disease. At such early stages, autoimmune diseases are associated with the presence, in a subject's serum, of tell tale antibodies to particular antigens characteristic of each particular disease, as is well known in the art; for example, antibodies to GAD or insulin in diabetes, antibodies to perinuclear factor and other proteins in rheumatoid arthritis and antibodies to myelin basic protein in multiple sclerosis.

As noted in the applicant's last response, such antibody markers are regularly used clinically in selecting candidates for therapeutic intervention, as for example the Diabetes Trials described in Yu et al., (2001), Diabetes, v. 50, pp. 1735-1740.

It is therefore well within the skill of those in the art to look for such prognostic indicators of autoimmune diseases and thereby to guide the appropriate timing of therapeutic intervention, without the difficulty postulated by the Examiner.

With respect to CD28 agonists other than anti CD28 agonist antibodies and agonist forms of B7-2, it is respectfully submitted that one of skill in the art is

enabled by the specification as filed to identify other CD28 agonists, using the assay methods described in the application.

¶9. Claims 1-2 were rejected under 35 U.S.C. §112, first paragraph, as allegedly not satisfying the written description requirement.

It is respectfully submitted that persons of ordinary skill in the art can recognise whether or not a molecule is a CD28 agonist based on the teachings of the specification.

Rejections Under 35 U.S.C. §103

¶11. Claims 1-6 and 8 were rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Rabinovitch (Diabetes (1994), 43, 613) and Lenschow et al. (Immunity (1996), 5, 285) in view of either King et al. (Eur. J. Immunol. (1995), 25, 587) or Webb et al., (Blood (1995), 86, 3479).

It is the Examiner's view that these references teach one of skill in the art that (a) stimulation of the CD28 receptor upregulates Th2 function and (b) upregulation of Th2 function is useful in preventing the onset of autoimmune diabetes.

The applicant respectfully disagrees and further submits that the prior art does not teach the utility of such Th2 function in preventing the onset of autoimmune diabetes.

With respect to *Rabinovitch*, the applicant submits that this publication discusses methods of using immunostimulation *in vivo* to prevent the onset of autoimmune diabetes. However, unlike the present invention, *Rabinovitch* indicate that non-specific immunostimulation by microbial extracts and adjuvants is capable of such anti-diabetic effect, and the only specific administration mentioned is by antigen presentation (of GAD65), rather than receptor activation (last paragraph, first column, page 619). Additionally, the authors suggest tat these aforementioned methods of immunostimulation are appropriate for clinical application to humans (1st paragraph, second column, page 619). In contrast, the present invention shows that specific

upregulation of the Th2 arm of the immune system is applicable to autoimmune disease therapy. Hence, an artisan with ordinary skill would have not been able to arrive at the present invention upon review of *Rabinovitch* and would have rather been motivated to immunize humans at risk of autoimmune diabetes with a general immunostimulatory agent, such as an adjuvant or microbial component, which would not specifically upregulate a Th2 type response. The applicant submits that *Rabinovitch* has illustrated that general immune stimulation is useful in treatment of autoimmune diabetes, rather than a method of specifically upregulating the Th2 arm of the immune response.

With respect to *Lenschow et al.*, the applicant submits that this reference further does not provide evidence that stimulation of CD28 signaling upregulates Th2 function in vivo. This publication illustrates that transgenic CD28-/- NOD mice have increased Th1 function in vivo (and consequently low Th2 function) and an accelerated onset of autoimmune diabetes. The present invention shows that **stimulation** of the CD28 signaling pathway is necessary to prevent the onset of autoimmune disease, and that the presence of CD28 surface protein alone is not sufficient thereto.

In addition, several aspects of these studies contradict the conclusion that upregulation of CD28 function in vivo would be sufficient to reverse the onset of autoimmune diabetes in unaltered NOD mice. Firstly, the authors indicate that their prior studies have illustrated that blocking B7-2 function in vivo, which would lower CD28-mediated signaling and function, has prevented the onset of diabetes in the majority of NOD animals (page 285, column 2, first full sentence, *Lenschow et al*). Hence, an individual of ordinary skill in the art would expect that upregulating B7-2 binding with CD28 would induce the onset of autoimmune diabetes, and hence contradict the findings of the inventors. Secondly, it is essential to note that the experimental conditions used by *Lenschow et al.* (1996) utilize a transgenic NOD animal with deletion of the CD28 gene, which also plays a highly influential role in maturation of T cells. Without CD28 function, Lenschow et al illustrate that the cytokine profile of CD28-/- T cells is remarkably different from corresponding T cells from the intact NOD mouse in terms of their stimulatory profile (page 286, last paragraph), and furthermore the response of such

T cells to various antigens was skewed in comparison to T cells from intact NOD mice (page 287, 1st paragraph). The applicant therefore contends that the transgenic CD28-/- NOD is unrepresentative of the autoimmune diabetes process that is regarded within the art to occur in NOD mice. Hence, the data illustrated by *Lenschow et al.* would not have convinced an individual of ordinary skill within the art and is contradictory to the evidence of the present invention.

With respect to *King et al.* and *Webb et al.*, the applicant respectfully disagrees with the examiner's opinion. While these two publications illustrate that treatment with anti-CD28 monoclonal antibodies leads to the secretion of Th2-type cytokine and the development of a Th2 phenotype, two features of these publications negate their applicability to the method of the subject invention. Firstly, these studies utilize *in vitro* conditions to illustrate the effect of anti-CD28 antibodies. As is well known within the art, several agents have been demonstrated to generate Th1 or Th2 *in vitro*, but have not produced the same effect in vivo. Examples of such discrepancy between in vivo and in vitro effects has been illustrated in IL-12 receptor blockade (Piccotti et al, (1997), J. Immunol., v. 158, pp. 643-8) and PDE-4 inhibitors (Bielikova et al, (2000), J. Immunol., v. 164, pp. 1117-24). Secondly, these studies are utilizing cell types that are distinctly different from the T cells relevant to autoimmune diabetes or any other autoimmune condition. *King et al.* utilize human peripheral blood mononuclear cells from normal individuals, while *Webb et al.* utilize naïve human CD4+ cells from umbilical cord samples. Therefore, one of skill in the art would not have been led to believe that the effect of anti-CD28 mAb in vivo would be to increase Th2 function in activated immune cells.

Accordingly, it is respectfully submitted that the claims are patentable over all of the cited art.

Allowable Subject Matter

Applicant respectfully submits that because claim 9 has been considered (see Office Action at ¶11) and does not stand rejected on substantive grounds, amended claim 9 is therefore in condition for allowance.

CONCLUSION

Attached hereto is a marked-up version of the changes made to the specification by the current amendment. The attached page is captioned "**Version with markings to show changes made.**"

For the Examiner's convenient reference, attached hereto is a reproduction of the claims presently under examination, captioned "**Claims presently under examination.**"

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 650-326-2400.

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

1. (Amended) A method for preventing the development of an autoimmune disease associated with increased Th1 immune cell activity in a susceptible subject comprising administering to the subject an effective amount of a T cell CD28 costimulatory receptor (CD28) agonist.

2. (Amended) The method of claim 3 [1] wherein the autoimmune disease is selected from the group consisting of autoimmune diabetes, multiple sclerosis, myasthenia gravis, rheumatoid arthritis, Hashimoto's thyroiditis, Sjogren syndrome and systematic lupus erythematosus.

9. (Amended) The method of claim 8 wherein the human subject is aged from about 6 months to about 2 or three years.

CLAIMS PRESENTLY UNDER EXAMINATION.

1. (Amended) A method for preventing the development of an autoimmune disease associated with increased Th1 immune cell activity in a susceptible subject comprising administering to the subject an effective amount of a T cell CD28 costimulatory receptor (CD28) agonist.

2. (Amended) The method of claim 3 wherein the autoimmune disease is selected from the group consisting of autoimmune diabetes, multiple sclerosis, myasthenia gravis, rheumatoid arthritis, Hashimoto's thyroiditis, Sjogren syndrome and systematic lupus erythematosus.

3. The method of claim 1 wherein the agonist is selected from the group consisting of an anti-CD28 agonist antibody, human B7-2 protein and a B7-2 extracellular domain polypeptide or an effective fragment of said polypeptide.

4. The method of claim 3 wherein the agonist is an anti-CD28 agonist antibody.

5. The method of claim 4 wherein the subject is a human subject.

6. The method of claim 5 wherein the antibody is a monoclonal antibody.

7. Canceled.

8. The method of claim 5 wherein the autoimmune disease is autoimmune diabetes.

9. (Amended) The method of claim 8 wherein the human subject is aged from about 6 months to about 2 or three years.

10-31. Canceled.